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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/654,850	09/04/2003	James A. Carnazza	18184-00001	5271

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EXAMINER	
KOLKER, DANIEL E	
ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 06/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/654,850	CARNAZZA, JAMES A.	
	Examiner	Art Unit	
	Daniel Kolker	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *2/21/06, 4/5/06*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,7,8 and 13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,7,8 and 13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1,7-8,13* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's remarks and amendments filed 21 February 2006 and 5 April 2006 have been entered. Claims 2 – 6, 9 – 12 are canceled; claim 13 is new. Claims 1, 7 – 8, and 13 are pending and under examination.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Rejections and Objections

3. The following rejections and objections made in the previous office action are withdrawn:

A. The objection to claim 1 is withdrawn in light of the amendments.

B. The rejection of claims 1, 6, and 7 under 35 USC 112, second paragraph is withdrawn in light of the amendments.

Rejections and Objections Maintained and Necessitated by Amendment

Oath/Declaration

4. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because: the filing date listed for provisional application is incorrect. The actual filing date is 4 September 2002, but the oath lists 4 September 2003 as the filing date. Correction is required. Applicant did not supply a new oath or declaration correcting the defect.

Priority

5. Applicant is advised that the instant application can only receive benefit under 35 U.S.C. § 120 or § 119(e) from an earlier application which meets the requirements of 35 U.S.C. § 112, first paragraph, with respect to the now claimed invention. As set forth in the previous office actions, neither of the provisional applications of which the instant application claims benefit teach the method claimed in claim 1. Therefore the effective filing date is set at the instant filing date, 4 September 2003. Should applicant argue that the provisional applications in fact are enabling disclosures, applicant should provide evidence of such, for example by pointing out the page and line numbers where the results of the experiments appear.

Applicant did not traverse the examiner's determination that the provisional applications do not disclose the claimed invention.

Claim Rejections - 35 USC § 112

6. Claims 1, 7 – 8, and 13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for determining whether or not estrogen binds to huntingtin protein in vitro, does not reasonably provide enablement for regulating estrogen, as encompassed by claims 1 and 7 – 8, or for regulating "certain hormone levels" as recited in new claim 13, or for determining an optimum time to begin regulation, or for determining if the levels of estrogen or other hormones are below normal for a given individual. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There are many factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue. These factors include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (FED. Cir. 1988).

In the instant case, the claimed invention encompasses regulation of hormonal levels in patients who "carry the Huntington's disease gene". While this of course is a very broad recitation, as it encompasses patients who carry any allele of the gene, whether or not said allele confers increased susceptibility to acquiring Huntington's, the method is directed towards regulation of estrogen testosterone, progesterone, and their respective precursors, as well as esters of estrogen broader in patients, or those susceptible to acquiring the disease. Bonelli et al. (2004. Expert Opin. Pharmacother. 5:767-776, of record) teach that the treatment of Huntington's disease is difficult and complex (see particularly p. 768, first paragraph of section 2 and p. 772, section 5), indicating that the level of predictability in the art is low. The specification discloses that estradiol binds with stronger affinity to huntingtin protein with 63 glutamines than to the protein with 47 glutamines, and with stronger affinity to the 47-glutamine protein than to the 23-glutamine protein (see p. 12).

The claimed invention is a method of regulating hormone levels *in vivo*. The specification discloses no data on levels of any hormone in normal patients, in Huntington's disease patients, or in persons carrying a mutant allele of the *huntingtin* gene with an abnormally large number of CAG repeats that renders such individual susceptible to acquiring Huntington's disease. There is no indication, in either the specification or the art of record, that estrogen levels differ at all between patients with Huntington's disease, those who do not have it but are susceptible to acquiring it, and those that have relatively few CAG repeats in the *huntingtin* gene and thus will not acquire the disorder. Thus it is not at all clear that estrogen levels even need to be regulated. Claims 1 and 13 both instruct the artisan to establish that a serum level of estrogen (claim 1) or other hormones (claim 13) is below normal in an individual. However, as there is no guidance as to what constitutes "normal" in any individual, the degree to which the "normal" levels vary with the number of CAG repeats within any gene, and no working examples of the normal levels, it would take undue experimentation on the part of a skilled artisan to determine what constitutes normal, and then to determine those doses of estrogen needed in order to maintain the estrogen at a normal level for any given individual. While the examiner concedes that measurement of hormones is within the skill of the artisan, determining whether or not an individual's hormone levels are below "normal for that individual" requires considerably more experimentation and research. One would have to know, a priori, what the normal levels of estrogen, testosterone, or progesterone are for that individual. Neither the specification nor the art of record discloses any changes in hormonal levels with increasing burden of Huntington's disease. The claims do not require, for example, any foreknowledge of hormonal levels before disease onset in an individual, and the specification does not disclose if there are any disease-related changes in hormone levels. Even assuming, for the sake of argument alone, that estrogen levels are lower in patients with Huntington's disease than those who are not genetically susceptible to it, that alone does not indicate that the estrogen level is *below normal for that individual*, as recited in claim 1. It only indicates that the normal levels differ between the two groups.

Both the independent claims also require the artisan to determine an optimum time to begin regulating estrogen levels in the subject. There is no guidance in the specification as to what time the patient should receive estrogen, nor is there guidance as to whether how one would begin to determine this. The specification presents the results of a single experiment, wherein it was demonstrated that there is some degree of interaction between estradiol and

huntingtin protein. There are no kinetic data presented, which would be important in determining factors relevant to time or frequency of administration, nor are there, for example, longitudinal data to demonstrate how the time of disease onset is related to the affinity of estradiol for huntingtin protein. The specification discloses (p. 12) the results of an experiment which indicate that estradiol binds more efficiently to longer poly-glutamine regions of huntingtin protein. The specification then discloses (p. 12, line 25) that this information is sufficient for a physician to determine the optimum time to begin therapy (note that the estradiol-binding assay is described as a preferred method for determining the optimum time for administration, see p. 6 first full paragraph). However, there is no disclosure or guidance as to which factors should be used to determine this time. If there are relatively few glutamine repeats, estradiol will not bind well, whereas more will be bound if there are more glutamines (see p. 12). The specification does not provide guidance as to how the timing of therapy should vary in accordance with the number of glutamines.

New claim 13 encompasses methods of administering progesterone or testosterone to an individual, but there is no disclosure of administration of either of these to an individual. There is no disclosure of how administering testosterone is related to the affinity of estrogen for huntingtin protein. As set forth in the previous office action, estrogen and testosterone are known to have opposite effects when administered to animals. Eckert (1988. Animal Physiology. pp. 314 - 318) teaches estrogen promotes the development and maintenance of female characteristics, whereas testosterone promotes the development of male characteristics. A skilled artisan would not expect the two compounds to be interchangeable, given their vastly different effects on mammals, and the lack of working examples of administration of either estrogen or testosterone or a precursor thereof to an individual. Applicant argues, on the final page of the remarks, that since Eckert teaches that the structures of estradiol, progesterone, and testosterone share certain common elements they would be expected to essentially be interchangeable. Applicant's arguments have been fully considered but they are not persuasive. There is no evidence in the specification or art of record that indicates that the steroid structure of estradiol is what allows it to bind to huntingtin protein. As Eckert (p. 315) shows, estradiol, testosterone, and progesterone have many structural differences, from the number of double-bonds in the ring structures to the various functional groups attached to the steroid backbone. Nothing in the specification teaches the artisan that the steroid backbone, rather than either the side chains or the structure of the molecule as a whole, permits binding to huntingtin protein. In fact, there are many physiological functions where one of these molecules cannot substitute for the other. Testosterone

directs development of embryonic tissues to a male fate (see Eckert, p. 314), whereas estrogen does not. Estradiol-17-beta (estrogen) regulates adult female reproductive cycles, whereas testosterone does not. Neither estrogen nor testosterone can take the place of progesterone in maintaining pregnancy. Clearly the structures and functions of these hormones are not interchangeable. As the specification only provides a single working example, in this case of estradiol interacting with huntingtin protein, and the art indicates that the effects of estradiol are not interchangeable with progesterone and testosterone, it would take undue experimentation for a skilled artisan to practice claim 13 over its full scope.

Claim 8 is drawn to a particular amount of radioactivity, expressed in counts per minute. The number of counts per minute of radioactivity in a sample is dependent on the amount of starting material (i.e. labeled estradiol in this case), the specific activity of the material, the amount of time that has passed since the starting material was labeled with the isotope, the isotope used, the sensitivity of the gamma counter, and the distance from the radioactive source to the counter. There is no disclosure of the specific activity of the starting material, the amount of time that had passed since the estradiol was labeled, the sensitivity of the counter, or the distance between the counter and the sample. A skilled artisan would thus have to resort to undue experimentation in order to replicate applicant's results expressed in counts per minute, as the artisan would have to manipulate multiple variables. Furthermore, because 50,000 cpm can be obtained simply by increasing the amount of starting material, an artisan would not conclude that said measurement is indicative of binding. Finally, the claim does not indicate whether the supernatant or pellet should be measured; in applicant's assay described on p. 12 of the specification the supernatant was counted, but the artisan would recognize that a large amount of radioactivity would remain in the pellet and column.

The scope of enablement bears little resemblance to the scope of the claimed invention. What is disclosed is a very narrow scientific discovery, namely that estradiol binds to huntingtin protein *in vitro*. There is no disclosure of how to determine an optimal time of administration of a hormone, nor is there disclosure of which patients have abnormally low estrogen levels, or even how to determine what constitutes a normal level for such a person. If the *in vitro* data hold up *in vitro*, one might expect that patients with expanded polyglutamine repeats within the huntingtin protein would have more estrogen bound to the protein and less circulating. But this does not mean that the level would be "below normal for that individual"; it may just mean that what is normal for one person is not normal for the next. Furthermore, any change in circulating estrogen levels would likely be quickly compensated for by the exquisitely sensitive regulatory mechanisms of the hypothalamic-pituitary-gonadal axis. There is also

no guidance as to the dosage of hormone to be administered, or the frequency that the hormone should be administered to maintain estrogen at a normal level for that person. Claim 13 encompasses any number of hormones, but the specification is only on point with respect to the ability of estradiol to bind to huntingtin protein. Thus for all the reasons set forth above, it would take undue experimentation on the part of a skilled artisan to practice the invention commensurate in scope with the claims.

In the remarks filed 21 February 2006, applicant addresses several of the examiner's concerns as to whether or not the claimed invention is enabled by the specification. However, applicant's comments are directed at an invention different from that which is now claimed. Applicant argues that since the specification shows that huntingtin protein is "bound up" by estradiol, the protein cannot exert its effects and therefore estradiol is a suitable treatment for HD. The claimed invention is no longer a method of treating HD, but rather is a method of regulating estrogen levels in a person who carries the Huntington's disease gene, thus the question of whether or not symptoms of the disease are ameliorated is not relevant.

7. Claims 1, 7 – 8, and 13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Amended claim 1 and new claim 13 both encompass administering estradiol (claim 1) or one of several hormones (claim 13) in amounts sufficient to maintain the hormone at a level normal for that individual. The examiner is unable to find support in the disclosure as originally filed for administration of hormones in amounts sufficient to maintain said hormones at those levels.

8. Claims 7 – 8 are is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 7 recites the limitation "said predetermining step" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim 8 is considered indefinite because it recites the limitation "equal to or less than about 50,000 counts per minute". This rejection was made in the previous office action. Applicant did not

address the examiner's assertion that recitation of 50,000 cpm is indefinite; thus the rejection stands for the reasons of record.

Conclusion

9. No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel Kolker whose telephone number is (571) 272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Daniel E. Kolker, Ph.D.
June 5, 2006

SHARON TURNER, PH.D.
PRIMARY EXAMINER
6-5-06